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32. The method of claim 31 wherein said autoimmune disorder is rheumatoid arthritis.--

REMARKS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Submitted herewith are declarations of Dr. Waldmann, Dr. Crowe and Dr. Johnston which are headed in parent Application No. 08/289,532. Entry of the declarations is requested.

The title has been revised to be more indicative of the present claims. The specification has been revised to introduce amendments presented in the parent case. The amendments do not raise the issue of new matter.

The original claims have been cancelled and new claims 18-32 have been added. The new claims, which are fully supported by an enabling disclosure, serve to define the invention with additional clarity. In considering the new claims, the Examiner is reminded that, in the interview held in connection with the parent case on February 21, 1996, the Examiner indicated that it was his view (as it is Applicants) that the inclusion in the

claims of the phrase "consists essentially of" does not raise the issue of new matter (see page 5 of Amendment responsive to November 14, 1995 Office Action).

The Examiner's comments regarding the drawings are noted and appropriate action will be taken in due course.

Claims 1-5 and 8-17 stand provisionally rejected as representing obviousness-type double patenting over claims 18, 19 and 30-36 of Application No. 08/298,532. In view of the provisional nature of this rejection, the Examiner is urged to hold it in abeyance until this case is otherwise in condition for allowance. The possibility of filing a terminal disclaimer to overcome the rejection is noted.

Claims 1-5 and 8-17 stand rejected under 35 USC 112, first paragraph. Withdrawal of the rejection is believed to be in order in view of the above-noted claim amendments, in view of the declaration evidence submitted herewith and further in view of the comments that follow.

The Examiner contends that "it is not clear from the specification whether non-depleting antibodies alone or in combination with depleting antibodies can generate tolerance to

all antigens or across all MHC barriers, in all species and, in particular, for transplantation antigens, autoantigens and immunoglobulin in humans." The Examiner relies on publications of Harris et al, Charlton et al, Russell et al, Nossal, Watson et al and Chen et al to support the notion that undue experimentation would be required to practice the present invention. Applicants respectfully disagree for the reasons that follow.

Enclosed with this Amendment is a declaration by Dr. Scott Crowe (originally filed in the parent case). Beginning on page 14 of his declaration, Dr. Crowe addresses the Examiner's concerns regarding enablement.

With regard to antibody therapy generally, Dr. Crowe points out that the confidence researchers have that antibodies will prove to be effective therapeutic agents is illustrated by the amount of time and money being spent by the pharmaceutical industry to develop therapeutic antibodies. The attachment to Dr. Crowe's declaration marked "JSC1" is a table listing over 150 antibodies currently undergoing evaluation as potential therapeutic agents. Over a third of these entries refer to Phase

I or Phase II clinical trials. As an illustration of a therapeutic antibody, Dr. Crowe mentions PANOREX, a murine monoclonal antibody which has been developed for the treatment of colorectal cancer. A Phase III clinical trial produced successful results and the antibody has been approved for marketing in Germany. Other Phase III clinical trials are ongoing.

The Examiner has relied upon a paper by Harris et al for the proposition that "there is little future for the use of rodent monoclonal antibodies for in vivo human therapy." This statement is belied by the fact that murine antibodies, such as PANOREX, are in development as therapeutic agents. The antibodies listed in the table of Attachment JSC1 include rodent, chimeric and humanized antibodies, and Dr. Crowe states that in his opinion, which he believes to be generally shared by those of skill in the art, all three types of antibodies have a place as therapeutic agents in humans. In view of the Examiner's concern that adverse reaction to antibodies represent a limitation to antibody therapy, Dr. Crowe then discusses two possible adverse reactions, xenosensitization and anti-idiotype reaction, and explains why

neither renders antibody therapy unusable. Patients are, and should be, monitored, and if an adverse response becomes a problem, an engineered antibody can be developed to reduce the problem.

The Examiner referred to a statement on page 42, right hand column, of Harris et al about anti-idiotype response. As Dr. Crowe points out on pages 17-18 of his declaration, what the authors actually said is that the HAMA response is greatly reduced for chimeric antibodies, that any response that remains is likely to be an anti-idiotype response and if such a response arises in a serious way, repeated dosing will be ineffective. Dr. Crowe does not disagree with this statement, but points out that Harris et al do not think that anti-idiotype response, which also can arise with humanized antibodies, is so much a problem that antibody therapy is rendered unusable.

On pages 19-21 of his declaration, Dr. Crowe addresses the Examiner's concerns regarding a number of additional references, specifically, the Russel, Nossel, Chen et al and Watson et al references. His comments are self-explanatory and no further comments appear warranted.

Applicants wish to highlight Dr. Crowe's statements in response to the Examiner's comments regarding the insufficiency of the murine examples provided in the subject application. Dr. Crowe points out on page 22 of his declaration that the mouse represents the best model available in the present circumstances and is a generally accepted starting point for immunological studies. Furthermore, the scientific literature now contains considerable evidence that the results in mice are predictive of the results in humans. Specifically, anti-CD4 mAbs have been used in the treatment of autoimmune conditions in animal models and in humans.

Dr. Crowe points out that the treatment of autoimmune conditions is a significant area where the induction of tolerance is advantageous and that a number of reports now have been published in the scientific literature relating to the use of anti-CD4 antibodies in animal models of autoimmune conditions. He points out that the experimental work of some researchers has effectively demonstrated that functional immune tolerance has been re-established following the administration of anti-CD4 antibodies. For example, Shimizu et al investigated the effect

of a depleting anti-CD4 antibody in the non-obese diabetic (NOD) mouse model (a mouse that spontaneously develops diabetes resembling human insulin-dependent diabetes mellitus (IDDM)). Dr. Crowe quotes from the paper:

> "We have been able to block the progression and subsequent expression of overt diabetes in NOD mice by a course of treatment with a monoclonal antibody to L3T4. Such an approach may be feasible for treatment of patients with subclinical manifestations of IDDM, since we show that antibody therapy initiated late in disease progression was effective in reversing islet cell destruction. Moreover, upon cessation of therapy the mice have remained disease free without further treatment.

Dr. Crowe also cites a paper by Hutching et al reporting on research using the same model but investigating the effect of a non-depleting anti-CD4 monoclonal antibody. These authors reported that the administration of non-depleting anti-CD4 antibodies provided NOD mice with long-lasting protection from the β cell destruction transferred by diabetic donor spleen cells and that responses to foreign antigens remains intact after the end of the antibody treatment. They further stated that their data suggest that tolerance to β cell antigens can be established

in mice already programmed to develop IDDM by administration of an anti-CD4 nondepleting antibody.

Importantly, the use of anti-CD4 antibodies in the treatment of autoimmune diseases in man is becoming well established, as indicated by Dr. Crowe. He notes that a literature search for references to the therapeutic use of anti-CD4 antibodies in man provided well over 100 references describing work on the treatment of various autoimmune conditions. Dr. Crowe summarized some of the significant review articles. Specifically, a review by Reithmuller et al.[1] discusses clinical data on the use of anti-CD4 antibodies in autoimmune condition in man and provides a summary of results in Table 2 of the paper. Dr. Crowe states that from these data he concludes that anti-CD4 antibodies have had at least some effect in all autoimmune conditions in man in which they have been tried.

[1] Reithmuller et al, "Human Murine Chimeric CD4 Monoclonal Antibodies: A Modern Panacea for Autoimmune Disease?", Immunological Series, Vol. 59, Monoclonal Antibodies and Peptide Therapy in Autoimmune Diseases, edited by J.F. Bach, pp. 261-269, of record.

Dr. Crowe also references a review in column 59 of Immunology Series by Morel[2] in which the authors state that anti-CD4 antibody therapy in the treatment of psoriasis has provided an "excellent clinical response" together with good tolerance in most patients who received the treatment. From this the authors conclude that anti-CD4 mAb may be a potential tool in the management of other severe dermatoses.

In addition, in a 1992 review by Reithmuller et al.,[3] the authors discuss a number of conditions, including rheumatoid arthritis, chronic inflammatory bowel disease, psoriasis, chronic immune hepatitis, polychondritis, uveitis posterios, myasthenia gravis and lupus erythematodes, and conclude that anti-CD4 antibodies have been effective in all autoimmune conditions in which they have been tried.

Dr. Crowe points out that in view of the dangers of profound immunosuppression in humans, it is highly preferable to treat autoimmune conditions by induction of tolerance rather than by

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[2] Morel et al, Immunological Series, Vol. 59, pp. 271-276, of record.

[3] Reithmuller et al, Immunological Reviews 1992, No. 129, pp. 81-104, of record.

immunosuppression. He notes that the doses which have been used up to now in man are considerably lower on a per kilogram basis than those which have been used in animals to induce tolerance. Dr. Crowe provides that in his opinion that good results are achieved in the treatment of autoimmune conditions in man, even though the work currently being undertaken involves sub-optimal doses. He states his belief that increased doses of anti-CD4 antibody will induce functional immune tolerance to autoantigens in the treatment of autoimmune conditions and that it presently is safe to predict that the induction of tolerance to autoantigens in the treatment of autoimmune conditions can be achieved in man by administration of non-depleting anti-CD4 antibodies in accordance with the teaching of this application.

In view of the animal data presented and the reasonableness of extrapolating from these results to the effectiveness of administering the antibodies to humans, Applicants respectfully submit that they have enabled the method of their invention.

The Examiner specifically questioned whether the data provided in this application, which is directed to certain specific antigens, has enabled the invention over the full range

of antigens claimed. Dr. Crowe addresses this point on page 26 of this declaration. He states that it is well-established that antigens differ in the response they evoke from the immune system; some antigens evoke a much stronger response than others. Although it may not be possible to induce tolerance to all antigens in all circumstances using the same protocol, Applicants have provided a basis for arriving at a means for inducing tolerance to a range of antigens using a protocol adapted to the antigen in question. From the guidance provided in the application, one of ordinary skill in the art could determine an appropriate protocol for establishing tolerance to a particular antigen. Dr. Crowe attests that although some experimentation may be necessary in each particular case, the amount of experimentation involved will not be undue.

Dr. Crowe makes specific reference to papers by Charlton et al. cited by the Examiner in support of his rejection. As Dr. Crowe points out, the research efforts of Charlton et al fall outside the scope of the present invention. He also points out that Charlton et al were seeking to induce tolerance to ovalbumin, a protein cleared very quickly from the circulation,

and that it thus is likely that all of the antigen would have been cleared from the body before a tolerance permissive environment was established.

In view of the above, reconsideration is requested.

Claims 1-5 and 8-17 stand rejected under 35 U.S.C. §112 on the basis that they are indefinite. Withdrawal of the rejection is believed to be in order in view of the above-noted claim amendments. Reconsideration is requested.

Claims 3-5 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Waldmann (Ann. Rev. Immunol.) or Qin et al. (J. Exp. Med.) Cancellation of the claims renders the rejections moot.

Claims 1-5 and 8-17 stand rejected under 35 U.S.C. §103 as unpatentable over Qin et al (J. Exp. Med. 1989) in view of Waldmann (Ann. Rev. Immunol., 1989 (hereinafter referred to as Waldmann I)), Waldmann (Am. J. Kid. Dis., 1988 (hereinafter referred to as Waldmann II)) and Cateron et al. Withdrawal of the rejection is submitted to be in order in view of the above-noted claim revisions and further in view of the comments that follow.

Qin et al relied upon the administration of bone marrow as a key element of their efforts to establish tolerance. In this regard, the Examiner's attention is directed to the present claims reciting "consisting essentially of". As Dr. Crowe explains beginning on page 2 of this declaration, the goal of Qin et al was to establish what they called "classical transplantation tolerance" in adult mammals. "Classical" in this sense refers to work of Medewar in the 1950s wherein tolerance in new-born mice was obtained by the injection of bone marrow. Qin et al sought to obtain the same type of tolerance in adult animals by priming the recipient with bone marrow which would express donor antigens. The donor antigens then would become autoantigens for the recipient. The recipient's immune system had to be suppressed to accept the bone marrow and the bone marrow then proliferated, expressing the majority of the antigens in the tissue to be transplanted. As the immune system of the recipient became repopulated, the lymphocytes began to consider the antigens on the transplanted tissue as self antigens. The result is that the lymphocytes are chimeric between the donor and recipient, a phenomenon known as hemopoietic chimerism.

In this situation, immunological tolerance is induced by the bone marrow transplant. The key thus is to get the bone marrow transplant established without it being rejected. Qin et al used antibody therapy as a means of immunosuppression to get the bone marrow transplant established. It is apparent from the Qin et al paper that the authors considered hemopoietic chimerism resulting from the bone marrow transplantation as an essential condition for the development of tolerance. The authors state:

> transplantation tolerance can, in a number of strain combinations, be induced in the adult mouse by *combining BM transplantation (BMT) together with parenteral administration of CD4 and CD8 mAbs*.

(page 779 (emphasis added)). Dr. Crowe quotes other passages of the Qin et al paper which further illustrate that the authors believed that bone marrow transplants, resulting in hemopoietic chimerism, was necessary to be able to achieve tolerance.

Thus, in view of this reliance upon bone marrow transplants, it is clear that the authors had no expectation that the administration of antibodies in the absence of the administration of bone marrow would induce tolerance. Indeed, it should be emphasized that in all of their experiments, the survival of skin

grafts was related to the ability of the antibodies to allow bone marrow transplants to become established so that the transplants then could establish tolerance. None of the antibodies (depleting or non-depleting, whole antibodies or fragments) was used in an effort to establish tolerance without bone marrow transplantation. The Examiner's attention is directed to Dr. Crowe's declaration, wherein he points out specifically how in each experiment the antibodies are used with bone marrow transplantation and that there is no suggestion anywhere in the Qin et al paper that antibodies alone could be administered to induce tolerance.

As noted above, Applicants have introduced amendments, where appropriate, to specify that the method of inducing tolerance claimed consists essentially of antibody treatment. In view of these amendments, the Qin et al paper is of little relevance. None of the secondary references compensates for the fundamental deficiency of the primary reference. Reconsideration is thus requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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